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Abstract

Electrophysiological measures appropriate for use in neurotoxicity testing of children are reviewed. These methods include sensory evoked potentials (auditory brainstem, pattern-reversal visual, somatosensory) and event-related slow potentials (contingent negative variation and association/P300 wave). Selection criteria, strengths and weaknesses of individual tests are discussed. Slow potential and auditory brainstem data from children exposed to lead are presented as examples.

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Neurotoxicity assessment in young children poses a considerable challenge due to language and behavioral constraints. Traditional psychophysical threshold, psychomotor, and cognitive tasks used in behavioral toxicology cannot reliably be administered to children below three to five years of age. On the other hand, this subset of the population is uniquely susceptible to neurotoxic impairment due to the immaturity of the nervous system. Development of an electrophysiological assessment battery that is free of linguistic and motor contraint would thus provide a useful contribution for neurotoxicity testing in young children.

Criteria to be considered in selecting pediatric neurotoxicity measures are listed in Table I. Neurotoxicity tests should meet the selection criteria required of psychometric tests --- i.e., each test should be standardized, valid, reliable, and objective. Most importantly, tests must be sensitive to the effects of toxicant exposure. Tests should also be noninvasive and non-threatening, culture-free and as age-independent as possible. Standard psychometric tests (e.g., IQ tests) are age-dependent and widely criticized as culturally biased. If the objective is population screening (as opposed to clinical evaluation), three additional criteria should be considered in test selection. Tests should be rapid (as a rule of thumb, the battery should be limited to about 30 minutes in length), simple to administer and score, and inexpensive.

Are there electrophysiological measures that meet these stringent criteria? Peripheral nerve conduction velocity (NCV) is the most widely used electrophysiological measure in human neurotoxicity testing. However, there is substantial doubt regarding the sensitivity of NCV measures in young children due to the wide range of "normal" variability. Other evoked brain potential measures have been clinically validated for the assessment of auditory, visual and somatosensory function in the central nervous system. These tests -- including the brainstem auditory (BAEP), pattern-reversal visual (PREP), and somatosensory (SEP) evoked potentials -- require no motor expression and minimal language comprehension. Each has achieved widespread clinical application during the past decade in the assessment of sensory pathway integrity and nonspecific demyelinating diseases such as multiple sclerosis (Aminoff, 1980; Desmedt, 1980; Starr, Sohmer & Celesia, 1978).

Otto (1983) and Arezzo, Simson & Brennan (1985) have reviewed the use of evoked potentials in occupational medicine and human neurotoxicity assessment. BAEPs, PREPs and SEPs have seldom been used for neurotoxicity testing in children and only meager evidence has been obtained in adults. Seppalainen (1978) compared the sensitivity of NCV and SEP as indices of subclinical neuropathy in lead workers. She reported that the SEP detected impairments at lower blood lead levels than NCV measures. Seppalainen, Raitta & Huuskonen (1980) used visual evoked potentials (VEP) in a study of workers exposed to n-hexane. VEP deficits were noted in 14 of 15 workers studied. VEPs are elicited by diffuse photic stimulation, while PREPs are elicited by a reversing checkerboard. PREPs are more sensitive than VEPs in diagnosing optic nerve degeneration and multiple sclerosis (Halliday, McDonald & Mushin, 1972, 1973).

Pattern-reversal FPs may, therefore, be more sensitive than flash FPs to toxicant substances that affect visual function.

Brainstem Auditory Evoked Potential

Figure 1 illustrates a typical BAEP. Note the time scale. Seven components occur within 10 msec of click onset. Successive components reflect the transmission of the afferent signal from the acoustic nerve to thalamus, each component reflecting a relay in the auditory pathway. Although the precise origins of these components are still debated (e.g., Scherg & Von Cramon, 1985) enough is known to accurately localize lesions in the auditory pathway. The variability of component latencies, particularly components I, III and V, is so small that a slight increase in component latency is indicative of pathology in the auditory pathway. Simple measures permit determination of central or peripheral levels of damage. Because the amplitude of BAEP components is usually less than 0.5 μV, a million-fold amplification and large number (2000-4000) of trials may be necessary to obtain adequate signal-to-noise resolution. Click stimuli can be presented rapidly (up to 50 Hz), however, so that an average may require less than one minute. For screening purposes, a click of about 30 Hz is recommended (cf. Schwartz & Berry, 1985).

The BAEP is remarkably robust and is not affected by arousal level -- e.g., a normal BAEP can be recorded in a comatose patient as long as the auditory pathway is intact (Starr 1977). Clinicians, in fact, prefer to record BAEPs in sleeping children to avoid electromyographic (EMG) artifact that accompanies movement (Jerger, Hayes & Jordan, 1980). Trials containing EMG artifact must be rejected, making it difficult to record from uncooperative children. In

clinical practice sedatives are usually administered to young children prior to recording BAEPs. We have found that most children can be coaxed to relax or fall asleep for BAEP testing without sedation (Otto, et al, 1985).

Figure 2 illustrates a useful maturational feature of the BAEP. Adult latencies are reached by the age of 18 months. BAEPs thus offer measures of peripheral and central auditory function that are practically age independent.

Evidence from studies of children with undue lead absorption (Otto, et al, 1985; Robinson et al, 1985) suggest, furthermore, that BAEPs are sensitive to heavy metal exposure. Latencies of peaks III and V (Otto et al, 1985) and interpeak latency V-I (Robinson et al, 1985) increased directly with blood lead levels as illustrated in figure 3.

Pattern-Reversal Visual Evoked Potential

Figure 4 illustrates a typical PREP. This waveform is elicited by a reversing checkerboard pattern in which dark and light squares alternate to maintain constant luminance levels. The PREP reflects activity primarily from the fovea (central three degrees of the visual field) because: (1) foveal cells project to the surface of the visual cortex, while peripheral retinal cells project to areas deep within the calcarine fissure; and (2) foveal representation in the cortex is disproportionately greater than peripheral visual projections (Sokol, 1980). The latency of the P100 component is sensitive to visual pathway lesions. Increased latencies indicative of optic neuritis or multiple sclerosis can be reliably detected prior to the emergence of clinical symptoms (Halliday et al, 1972, 1973). Since many neurotoxicants affect visual function (see Table II), the PREP is a recommended component of a neurotoxicity

test battery.

Important features of the PREP waveform vary systematically with stimulus intensity, check size, presentation rate, retinal locus of stimulation, and quality of the display. Detailed consideration of these methodological factors is beyond the scope of the present discussion, but excellent reviews are available (Desmedt, 1977; Sokol, 1976; 1980). To summarize briefly, P100 amplitude decreases and latency increases as pattern intensity (luminance) or optical quality decreases. Smaller checks tend to elicit more complex waveforms than larger checks at slow presentation rates. A transition from a multi-peak to a single-peak waveform (called a steady state potential) occurs at alternation rates between six and ten per second, depending on check size (figure 5). Since the PREP reflects cone activation, selective parafoveal stimulation does not elicit a clearly defined waveform.

Several subject parameters including pupil size and level of light adaptation also affect P100 amplitude and latency. Pupil size controls retinal luminance. In particular, clinical disorders such as glaucoma, medications, or adaptation levels that produce miosis (pupil constriction) depress amplitude and increase latency of the P100 component. It is thus important to check pupil diameter at the time of testing. The test should not be run if pupils are miotic or dilated. For neurotoxicity testing, the stimulus parameters noted above, pupil diameter, and the level of light adaptation must be rigorously standardized across subjects.

P100 latency also varies with age, an important factor in assessing

pediatric populations. Sokol and Jones (1979) have shown that P100 latency decreases rapidly during the first year of life and then slowly until about five years of age (figure 6). The latency x age function varies also with check size. P100 latency matures earlier for large checks than small checks. Little change in P100 latency occurs after six months of age for check sizes 30 minutes of arc or larger.

PREP-testing of young children is difficult because it is necessary to fixate on a reversing checkerboard for several minutes. Each average requires 100-200 reversals at a rate of about two per second. At least two averages should be obtained for each test to assure reliability. If each eye were tested separately, the complete test would require about eight minutes of fixation, assuming the use of a single check size and single stimulus rate.

Young children do not tolerate eye patches well. Monocular recordings in young children are thus difficult to obtain. Since lead (and other neurotoxicants) produce diffuse, nonspecific effects on CNS function, our PREP protocol included two binocular tests only. Inconsistent findings in two samples of children at risk for lead poisoning (Otto, et al, 1985; Otto, 1985), however, indicate the need for further study to determine the optimal stimulus parameters for neurotoxicity testing.

If toxicant exposure impairs scotopic (rod-mediated) vision more than photopic (cone-mediated) vision, the PREP waveform is unlikely to be affected since it reflects cone activation. Lead and carbon monoxide (McFarland, Roughton, Halperin & Niven, 1944; Sillman, Bolnick, Rosetti, Haynes & Walter, 1982) both appear to show more pronounced effects under dark-adpated (scoptic) conditions. Flash evoked potentials (Wooten, 1972) or contrast-sensitivity (Arden, 1978) methods may provide better visual function tests in these cases.

Assessment of Somatosensory Function.

In some respects the somatosensory system is ideal for neurotoxicity testing. Somatosensory pathways, stretching from the hands and feet to the cortex, are extremely long and can be assessed with noninvasive electrophysiological methods as different levels of synaptic transmission. Peripheral nerve conduction velocity (NCV) has long been used by neurologists to diagnose peripheral neuropathy in workers exposed to lead and other toxic chemicals (Seppalainen, 1975). Arrival of the afferent signal in somatosensory cortex can be recorded also from scalp electrodes using signal averaging procedures. Newer evoked potential techniques have been to assess neurological disorders in the spinal cord, brainstem, and thalamus (Noel & Desmedt, 1980).

Despite widespread use of somatosensory evoked potentials (SEPs) in clinical neurology, little effort has been made to apply SEPs in human neurotoxicity assessment. Seppalainen (1978) reported that the scalp-recorded SEP was more sensitive than NCV as an index of subclinical neuropathy in lead-exposed workers. Arezzo, Schaumburg, Vaughn, Spencer & Barna, 1982) reported that SEP changes preceed behavioral or NCV alterations in monkeys exposed to acrylamide. Schaumburg, Arezzo, Markowitz & Spencer 1981) noted some problems that confront the application of SEPs in human neurotoxicity testing: waveforms vary with age, skin temperature, body size, and location of scalp electrodes. The noxious nature of electric stimuli may be problematic in pediatric testing. The potential versatility and sensitivity of the SEP, however, argue for inclusion of this measure in a general neurotoxicity screening battery.

Figure 7 illustrates a method described by Eisen and Odusote (1980) to measure central and peripheral conduction time following median nerve stimulation.

Surface electrodes are placed at several convenient anatomical landmarks that permit the derivation of central and peripheral components. The stimulating electrode(s) is attached at the wrist over the median nerve. Peripheral conduction time between the wrist and brachial plexus is obtained by recording from an electrode at Erb's point in the supraclavicular fossa referred to the mastoid process. The initial component of the Erb's point potential reflects the arrival of the afferent volley in the brachial plexus. Peripheral conduction time recorded in this manner from normal, healthy adults is 8.9 ± 0.7 msec.

Central conduction time from dorsal column nuclei to cortex is derived from two other measures. Arrival of the sensory volley in the dorsal column nuclei is reflected in the N14 component of the cervical SEP. The cervical SEP is recorded from an electrode (C7) place at the base of the neck between the 6th and 7th cervical spines. C7 is referenced to a midfrontal (Fpz) lead. Arrival of the afferent volley at the cortex is reflected in the N20 component of the SEP recorded over contralateral somatosensory cortex (C3 or C4) referred to Fpz. Central conduction time from dorsal column nuclei to cortex is calculated as the difference (N20-N14) between the cortical and cervical components. The value obtained by Eisen and Odusote (1980) from normal, healthy adults is 5.1 ± 0.6 msec.

The maturation of the somatosensory evoked potential has been studied by Desmedt, Brunko, and Debecker (1976,1980). These investigators described the developmental course of the N22 component evoked by finger stimulation. This component is analogous to the N20 component elicited by median nerve stimulation. The developmental pattern, illustrated in Figure 8, is complicated by the fact that peripheral and central segments of the lengthy pathway mature at different rates, and that SEP latency depends on body size

(nerve length) which varies greatly during development. Body size and N22 latency normalized for body size are plotted in figure 8b. The normalized latency decreases sharply during the first 18 months, then decreases slowly to about eight years of age. Peripheral afferent axons mature rapidly during the first year (Gamstorp & Shelburne, 1965). Figure 8a exhibits the constancy of N22 onset latency from six months to eight years. Considerable work is needed to establish the maturational course of SEP components recorded at different synaptic levels of the somatosensory pathway.

Event-Related Slow Potentials.

In addition to sensory evoked potentials, there is another family of electrophysiological measures related to information processing , cognition, and memory. These waveforms are collectively called Event-Related Slow Potentials (ERSPs) or association potentials. The three most prominent ERSPs are: (1) Contingent Negative Variation (CNV) -- a slow vertex-negative shift in scalp-recorded EEG that arises during a signalled reaction-time foreperiod (Walter, Cooper, Aldridge, McCollum & Winter, 1964); (2) Readiness Potential (RP) -- a slow vertex-negative shift in EEG baseline that arises about one second prior to a stereotyped movement (Kornhuber & Deecke, 1965); and (3) P300 -- a large positive wave that peaks 300-900 msec following a stimulus that delivers relevant information to the perceiver (Sutton, Braren & Zubin, 1965). Preliminary efforts to apply ERSP methods in environmental toxicology have been reviewed by Otto and Reiter (1978). Groll-Knapp, Wagner, Hauck & Haider, 1972) reported a dose-related decrease in CNV amplitude in subjects exposed to low concentrations of carbon monoxide, although the same laboratory (Groll-Knapp, Haider, Hoeller, Jenker & Stidl, 1978) was unable to replicate these results. Otto, Benignus & Prah (1978) reported a paradoxical increase in CNV amplitude in subjects exposed

to 100 ppm CO, but a decrease in subjects exposed to 200 ppm CO.

The sensitivity of ERSPs to neurotoxicant exposure in children has been demonstrated in a series of studies (Otto, Benignus, Muller & Barton, 1981; Otto, Benignus, Muller, Barton & Schroeder, 1982 Otto et al, 1985). A linear relationship between slow wave voltage and blood lead level (figure 9) was observed in young children during passive sensory conditioning (Otto et al, 1981). Slow wave voltage varied systematically across the observed range of blood lead levels (6-59 ug/dl) -- evidence that Pb exposure alters CNS function at levels below the 25 ug/dl limit currently considered to be "safe" (CDC 1985). The same relationship of slow wave voltage and PbB was observed in a two-year follow-up (Otto et al, 1982), but not in a five-year follow-up (Otto et al, 1985) study of the same group of children.

In the latter study, however, a linear increase in slow wave negativity with increasing lead exposure history was found (Figure 10) when a motor response requirement was added to the sensory conditioning test. Larger slow brain potentials were obtained during active than passive testing. The active test also appears to be more sensitive than the passive test to toxicant exposure, although it cannot be used in children below the age of four or five years. See Otto (1985) for further discussion of this problem.

While the pediatric lead studies provide encouraging evidence of the utility of ERSP measures in environmental toxicology, ERSPs must be considered as experimental measures. Although the relationships among ERSPs, behavior, and cognitive processes have been exhaustively explored during the past decade (cf. McCallum & Knott, 1973, 1976; Callaway, Tueting & Callaway, 1977; Otto, 1978; Kornhuber & Deeke, 1980), very little is known about the anatomical, physiological, or chemical substrate of these waveforms. Even the psychological and behavioral

significance of ERSPs remains a subject of lively controversy. Little effort has has been made to standardize testing procedures or to construct population norms for any ERSP measures. Most CNV tests employ a motor response such as key pressing, while the most popular P300 test requires counting -- factors that limit the use of these measures in young children.

Other methodological problems limit the application of ERSP methods in environmental toxicology, particularly in the assessment of young children. Eye and body movements produce artifacts during ERSP recording. Trials in which eye or body movements occur must be rejected from signal averages. Eye fixation on the stimulus generator is usually required to minimize eye movement artifact. The use of video cartoons to maintain eye fixation and cooperation of children has proven to be successful with children 30 months and older (Otto, Benignus, Seiple, Loiselle & Hatcher, 1980), but ERSP testing of children aged 6-30 months of age remains problematic.

Conclusions.

Salient features and limitations of several sensory evoked potentials that are widely used in clinical neurology and event-related slow potentials that are promising experimental measures have been described. To compare the relative merits of different electrophysiological measures as components of a pediatric neurotoxicity testing battery, each has been evaluated using the criteria specified at the outset. Table III indicates the ratings assigned to each measure with IQ included for comparison: plus (+) indicates that the measure meets the selection criteria; minus (-) indicates that the measure does not; a question mark (?) indicates that insufficient evidence is available to assign a rating. While this binary rating scheme is crude and little evidence exists to evaluate the sensitivity or utility of these tests in pediatric populations exposed to environmental toxicants, Table III provides a systematic

basis to select appropriate electrophysiological measures for neurotoxicity assessment. Clinically validated tests (BAEP, PREP, and SEP) of sensory dysfunction and non-specific demyelinating diseases must be considered as prime candidates. Event-related slow potentials including the CNV and P300 have considerable promise, but require modification, standardization, and validation to satisfy the selection criteria for a pediatric neurotoxicity test battery.

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FIGURE LEGENDS

Fig. 1 A typical brainstem auditory evoked potential with presumed origins of successive components.

Fig. 2 Latency of wave V response to 60-dB SL click as a function of age. A systematic decrease in latency occurs from birth to about 18 months of age. Each point represents an average of at least three measurements for individual subjects. (Redrawn from Hecox and Galambos, 1974).

Fig. 3 Scatter plots, regression lines, and 95% confidence limits of (a) hearing threshold (Robinson et al, 1985), (b) BAEP wave latencies of boys and girls (Otto et al, 1985), and (c) BAEP interpeak V-I latencies of children (Robinson et al, 1985) as functions of blood lead levels. Hearing thresholds were determined audiometrically using a 2 KHz pure tone. Linear increases in hearing threshold, latencies of BAEP waves III and IV, and V-I interpeak latency were observed with increasing blood lead concentrations.

Fig. 4 Pattern-reversal visual evoked potentials recorded from a six year old boy. Replicate waveforms were obtained using binocular stimulation from black and white squares subtending 24° visual angle, 90% contrast, and reversing twice per sec. Latencies of N1, P1 and N2 components and N1P1 amplitude were measured.

Fig. 5 Pattern reversal VEPs in response to 12 minute checks for different alternation rates. Alternation rate per second is shown to the left of the records. Note the change from transient to steady state VEPs between 6 and 10 reversals per second. (Redrawn from Sokol, 1980).

Fig. 6 Latency of P100 component for 15' checks as a function of age from infancy to adulthood. The curve was derived by least squares fit. (Redrawn from Sokol and Jones, 1979).

Fig. 7 Procedure to derive central and peripheral conduction times in somatosensory pathways following median nerve stimulation. (Adapted from Eisen and Odusote, 1980).

Fig. 8 Onset latency of the N22 negative cortical component as a function of postnatal maturation in normal children in the waking state. Upper section: Data from 39 newborns in REM sleep appear as a single point to the left abscissa zero. Each data point represents an average of at least 3 SEPs from an individual child. Data from 16 normal adults appear on the right (mean and SD). Onset latency of N22 in msec. Lower section: body length (cm) with the corresponding scale on the right and onset latency of N22 divided by body length (msec/cm) with the corresponding scale on the left. (From Desmedt et al, 1976).

Fig. 9 The relationship of blood lead level and slow wave voltage and during passive sensory conditioning: (a) Summary average of slow potentials recorded from the vertex of children aged 1 to 6 years. Mean voltage of the slow wave during a 1 sec epoch preceding shutter closure was computed. (b) Interactive effects of age and blood lead levels on slow wave voltage. Predicted slow wave voltage and 95% confidence limits are depicted as a function of original blood lead levels at the extreme ages of subjects. (Adapted from Otto et al, 1981).

Fig. 10 Slow potential amplitude at frontal (Fz), central (Cz) and parietal (Pz) scalp locations recorded during active sensory conditioning and plotted as a function of blood lead (PbB) levels of children on the day of testing. Slow wave negativity increased linearly with current PbB at all recording sites. Mean slow potential voltage during the half-second preceding the imperative stimulus was measured. Scatter plots of data from individual subjects are shown with 95% confidence intervals for derived regression lines. (Redrawn from Otto et al, 1985).

TABLE I. SELECTION CRITERIA FOR PEDIATRIC NEUROTOXICITY TESTS

1.	NON-VERBAL	test does not require verbal instruction or verbal response
2.	NON-MOTORIC	test does not require any voluntary motor response
3.	NON-INVASIVE	test does not require skin penetration
4.	NON-THREATENING	test does not frighten or upset children
5.	AGE-INDEPENDENT	test scores vary minimally with age
6.	CULTURE-FREE	test scores do not vary with ethnic background or social class
7.	STANDARDIZED	standard procedures for test administration and measurement have been developed, published, and accepted by user community; normative data available for evaluation of clinical significance of data
8.	VALID	test measures the dimension or function that it was selected to assess
9.	RELIABLE	test provides comparable results when administered on repeated occasions
10.	SENSITIVE	test discriminates between exposed and non-exposed populations; detects change at minimal effect threshold
11.	OBJECTIVE	test provide a quantitative measure that is not susceptible to subjective measurement bias
12.	RAPID	for population testing, individual measures should require no more than 10 minutes to minister; rapid scoring of response is also important
13.	SIMPLE	test should be simple to administer, simple for the subject to perform, and simple to score
14.	INEXPENSIVE	cost of test materials, administration and scoring within reasonable limits

TABLE II. SUBSTANCES TOXIC TO THE VISUAL SYSTEM IN HUMANS

Absinthe	Lindane
Antirabies	Mercuric chloride
Arsenicals (organic)	Methanol
Bee sting	Methyl acetate
Carbon dioxide	Methyl bromide
Carbon disulfide	DL-Penicillamine
Carbon Monoxide	Phosphorus
Carbon tetrachloride	Quinine
Cassava	Snake venoms
Clioquinol	Streptomycin
Cobalt chloride	Tetraethyl lead
Cyanide	Thallium
Dinitrotoluene	Tobacco smoke
Dinitrotoluene	Trichlorethylene
Disulfiram	Trinitrobenzene
Ergot	Trinitrotoluene
Ethylene glycol	Vincristine
Hexachlorophene	Wasp sting
Lead	

[a]Evidence indicates that these substances affect either intraretinal neurons or optic nerve fibers (Grant, 1980).

TABLE III. SELECTION CRITERIA FOR PEDIATRIC NEUROTOXICITY TESTS

	IQ	BAEP	PREP	SEP	SW	CNV	P300
(1) NON-VERBAL	–	+	+	+	+	–	?
(2) NON-MOTORIC	–	+	+	+	+	–	+
(3) NON-INVASIVE	+	+	+	+	+	+	+
(4) NON-THREATENING	+	+	+	+	+	+	–
(5) AGE-INDEPENDENT	–	+	+	+	–	–	–
(6) CULTURE-FREE	—	+	+	+	+	?	?
(7) STANDARDIZED	+	+	+	+	–	–	–
(8) VALID	+	+	+	+	?	?	?
(9) RELIABLE	+	+	+	+	?	?	?
(10) SENSITIVE	–	+	?	?	+	?	?
(11) OBJECTIVE	+	+	+	+	+	+	+
(12) RAPID	–	+	+	+	–	+	+
(13) SIMPLE	–	+	+	–	–	+	+
(14) INEXPENSIVE	+	–	–	–	–	–	–

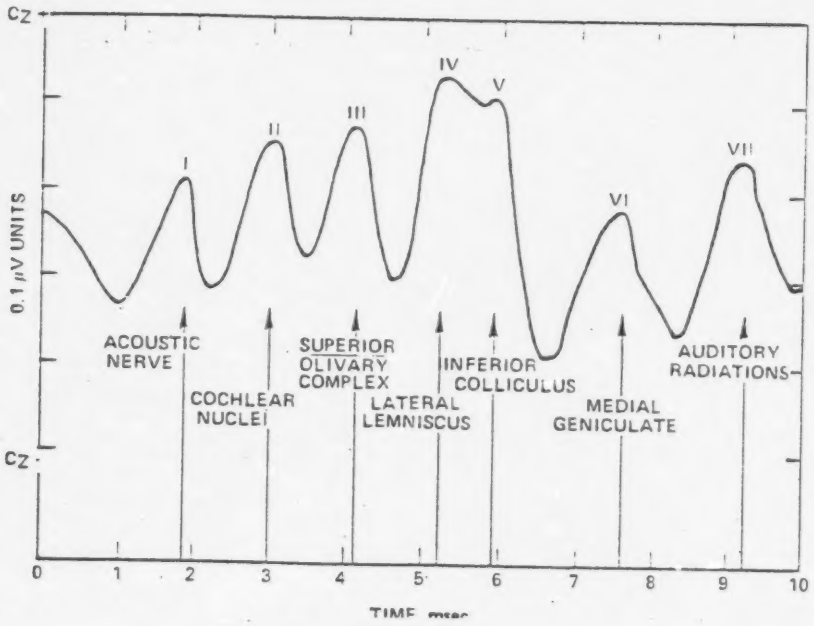


Figure 1

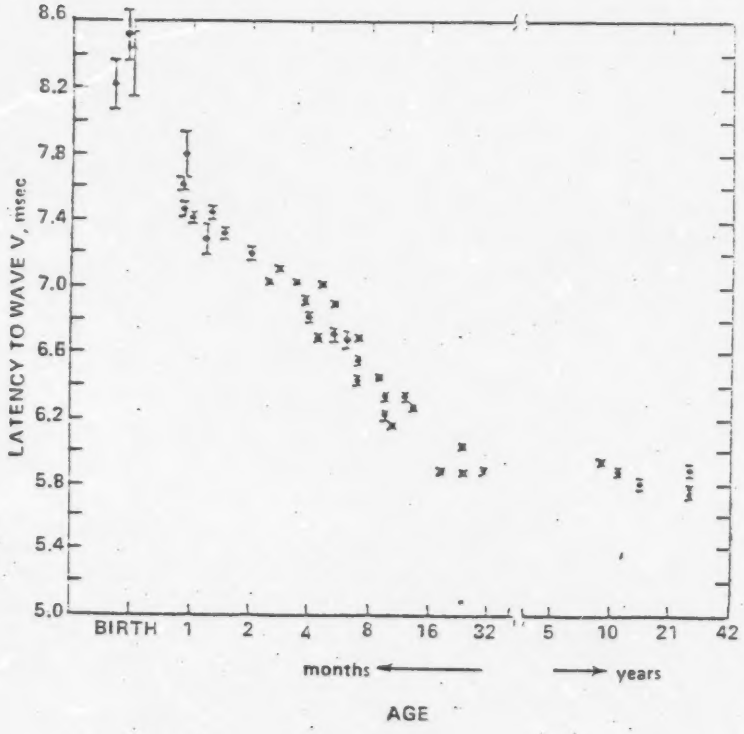


Figure 2

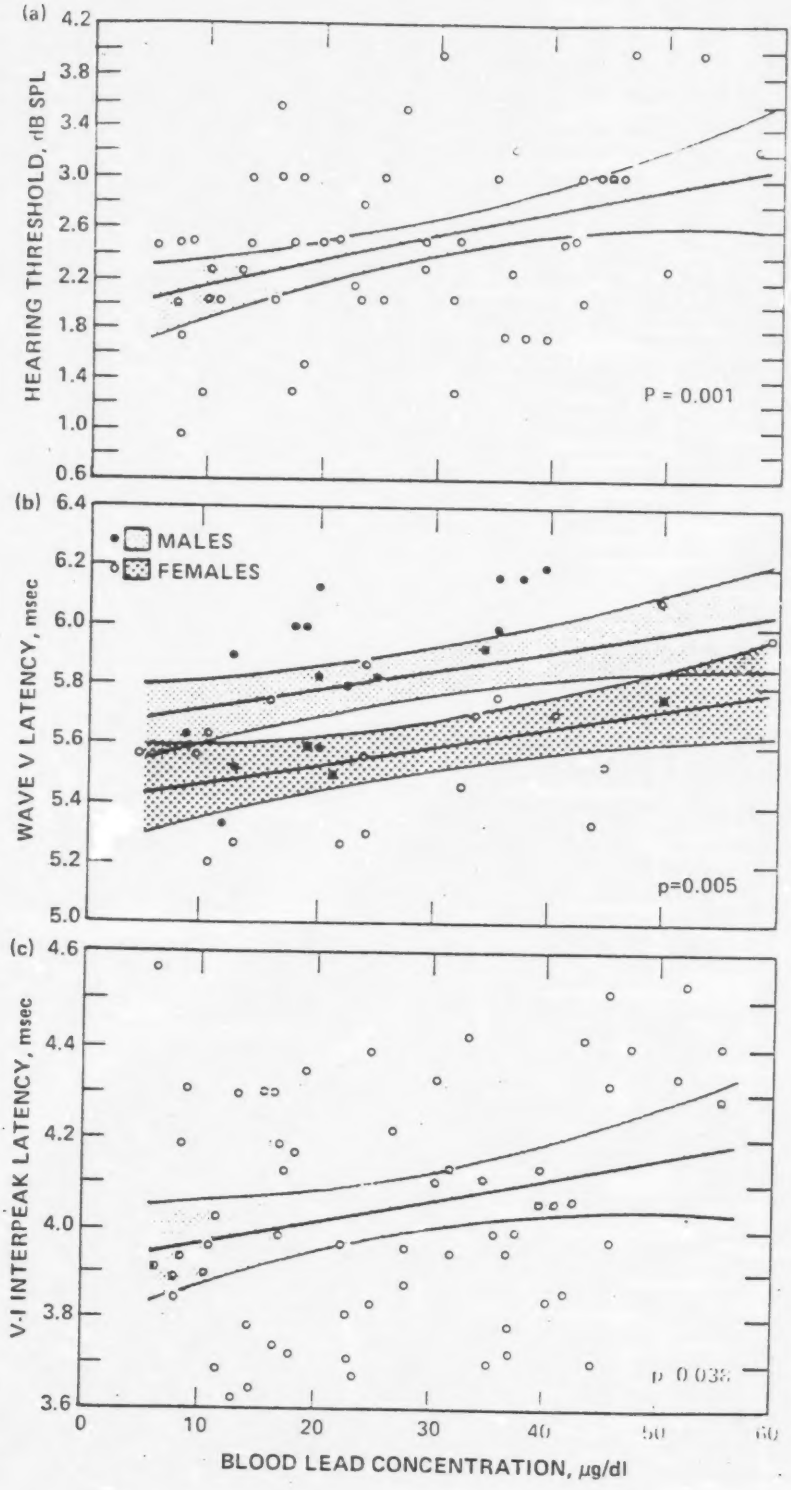
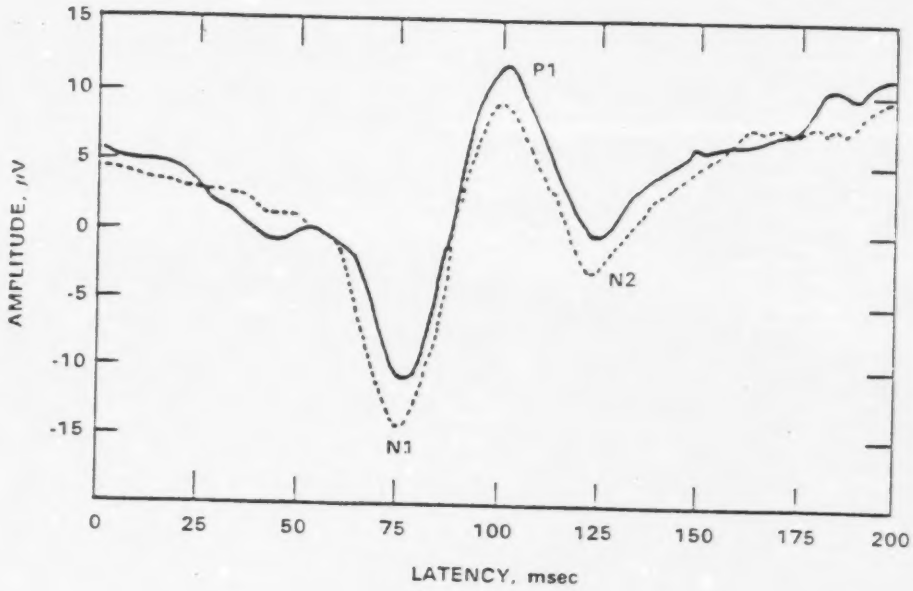

(a)
HEARING THRESHOLD, dB SPL
P = 0.001
(b)
MALES
FEMALES
WAVE V LATENCY, msec
p=0.005
(c)
V-I INTERPEAK LATENCY, msec
BLOOD LEAD CONCENTRATION, µg/dl

Figure 3



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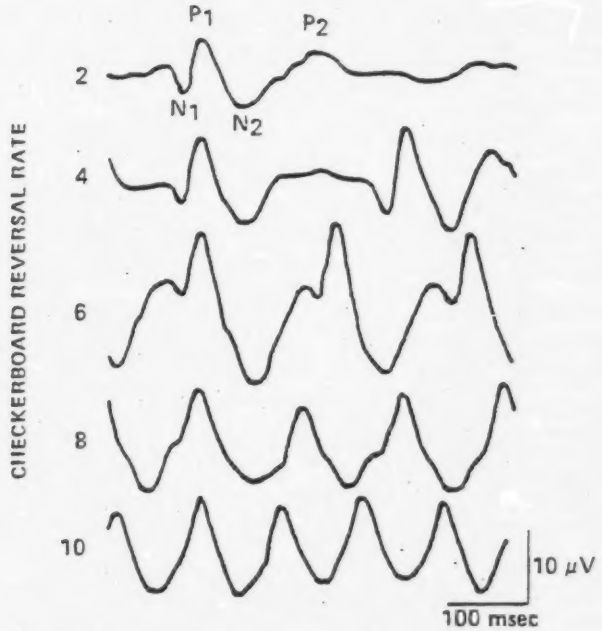

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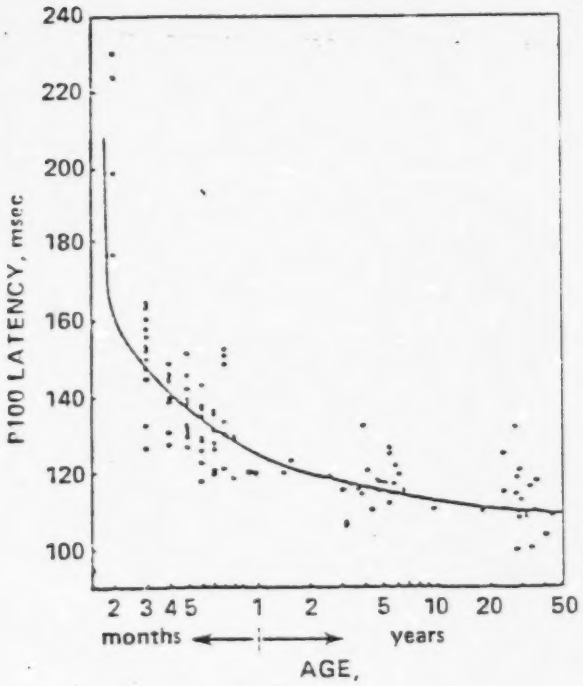
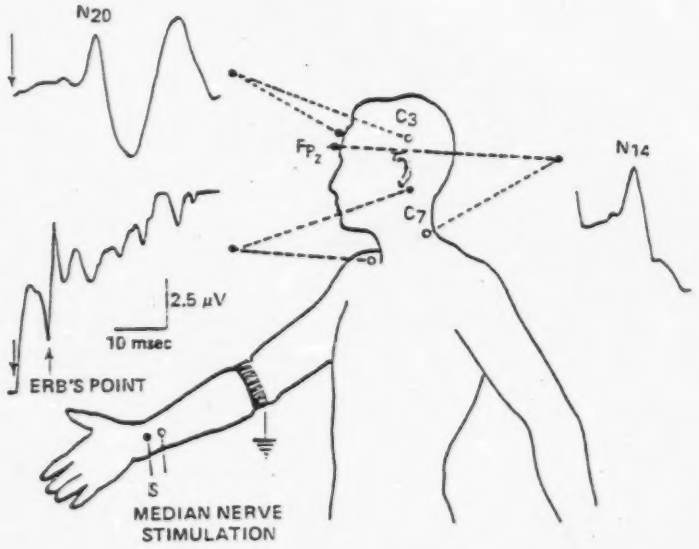


Figure 6



PERIPHERAL CONDUCTION TIME = LATENCY OF ERB'S POINT
CENTRAL CONDUCTION TIME = N_{20}-N_{14} LATENCY DIFFERENCE

Figure 7

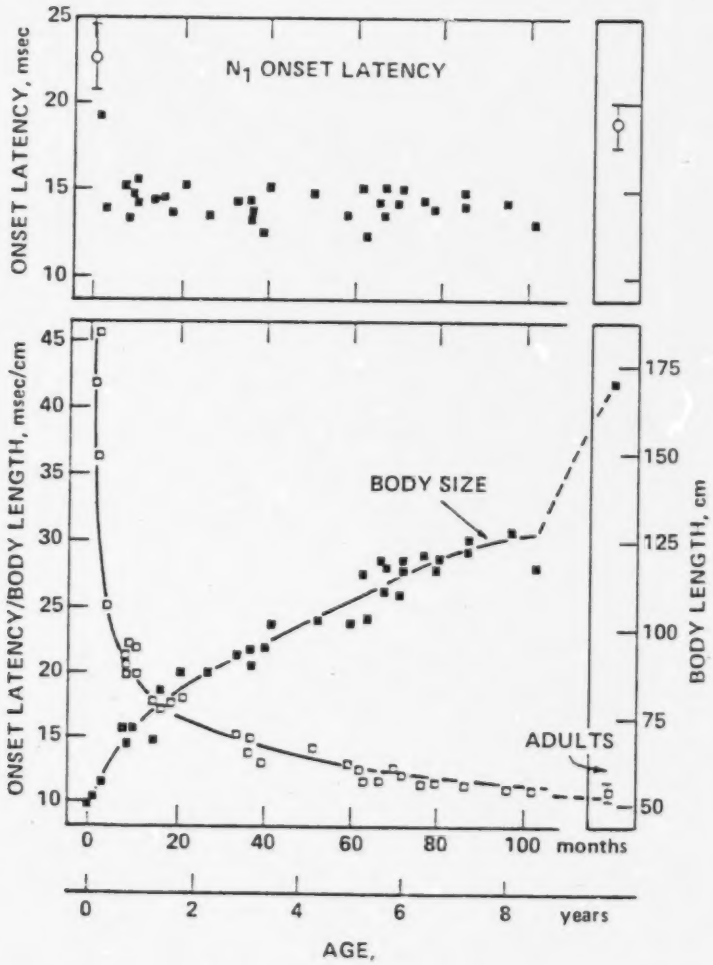
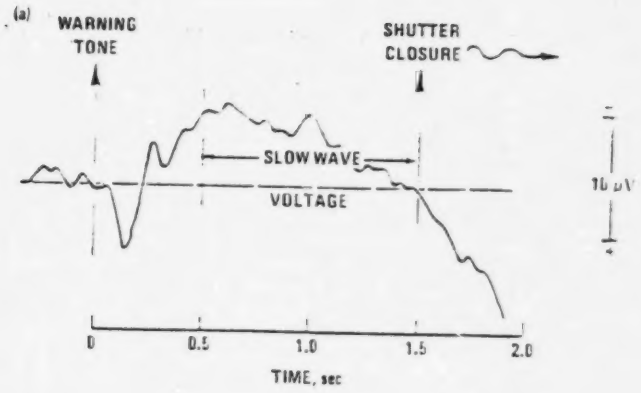

N1 ONSET LATENCY
ONSET LATENCY, msec
25
20
15
10
ONSET LATENCY/BODY LENGTH, msec/cm
45
40
35
30
25
20
15
10
BODY SIZE
ADULTS
BODY LENGTH, cm
175
150
125
100
75
50
0
20
40
60
80
100
months
0
2
4
6
8
years
AGE,

Figure 6



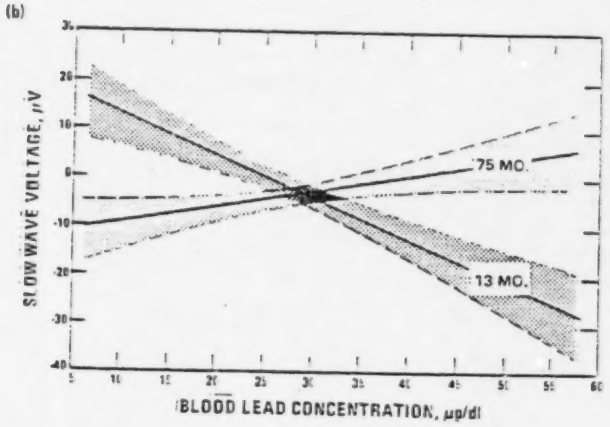


Figure 9

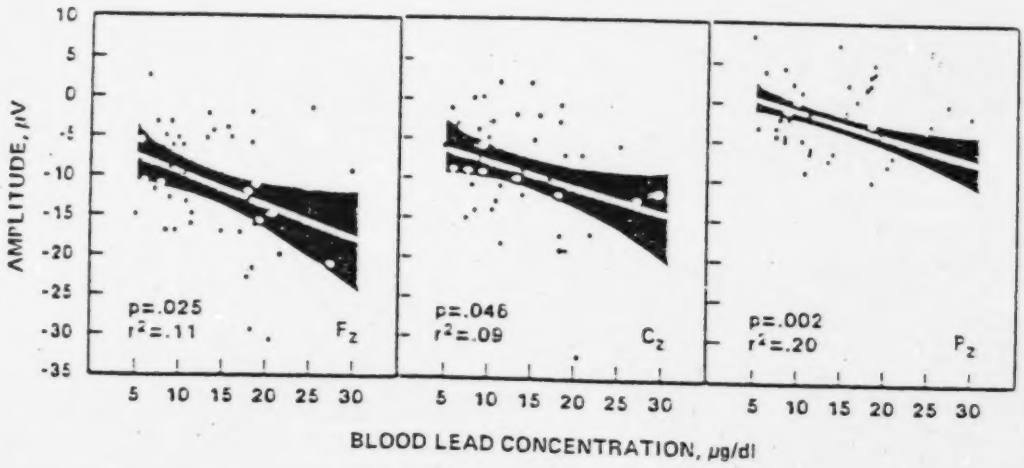


Figure 10